Razvan®

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Risperidone

DESCRIPTION:
Razvan® (Risperidone) is an antipsychotic agent belonging to a new chemical class of benzisoxazole derivatives.
Inactive ingredients:
Solution: Tartaric acid, benzoic acid (E210), hydrochloric acid, purified water.
Tablets: Maize starch, sodium laurilsulfate, hypromellose, lactose monohydrate, microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate, titanium dioxide, macrogol, sunset yellow FCF (E110)/ **Razvan®** 2 mg Iron oxide yellow (E172)/ **Razvan®** 3 mg & 4 mg.

PHARMACOLOGY:
Risperidone is a selective monoaminergic antagonist, it has high affinity for serotonergic 5-HT_2 and dopaminergic D_2 receptors. Although risperidone is a potent D_2 antagonist which improves the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics.
Risperidone is well-absorbed after oral administration, reaching peak plasma concentration within 1 to 2 hours. The absorption is not affected by food, so it can be administered regardless to meals. Risperidone is metabolized by the liver by cytochrome P450 IID6 to a major active metabolite 9-hydroxyrisperidone. Risperidone is rapidly distributed; the volume of distribution is 1-2 L/Kg. The plasma protein binding for risperidone is 88%, and that for 9-hydroxyrisperidone is 77%.

INDICATIONS:
Razvan® is indicated in the following cases:
- Treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive symptoms (hallucinations, delusions, hostility, thought disturbances, suspiciousness) and/or negative symptoms (blunted affect, social and emotional withdrawal, poverty of speech) are prominent.
- Alleviation of affective symptoms (depression, guilt feelings, anxiety) associated with schizophrenia.
- Maintenance of the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
- Treatment of conduct and other disruptive behavior disorders in children, adolescents and adults with subaverage intellectual functioning or mental retardation in whom destructive behaviors (e.g. aggression, impulsivity and self-injurious behaviors) are prominent.

CONTRAINDICATIONS:
Razvan® is contraindicated in patients with known hypersensitivity to the product.

SIDE EFFECTS:
Risperidone is generally well-tolerated.
Common side effects:
Insomnia, headache, anxiety, agitation.
Sedation, which is usually mild and transient, has been reported more frequently in children and adolescents than in adults.
Less common side effects:
- Somnolence, fatigue, dizziness, impaired concentration, nausea, vomiting, constipation, dyspepsia, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.
- Risperidone has lower potential to induce extrapyramidal symptoms than classical neuroleptics. However, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. These side effects are usually mild and reversible upon dose reduction and/or administration of antiparkinson medicine, if necessary.
- Occasionally, orthostatic hypotension and reflex tachycardia or hypertension. A decrease in neutrophil and/or thrombocyte count has been reported. Weight gain, edema and increased hepatic enzyme levels. Risperidone can induce a dose-dependant increase in plasma-prolactin concentration. Possible associated manifestations: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhea.
- Cerebrovascular adverse events, including cerebrovascular accidents and transient ischemic attacks, have been reported during treatment with risperidone.
- Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment.
- As with other neuroleptics, the following symptoms may take place: water intoxication due to either polydipsia or the syndrome of inappropriate secretion of antidiuretic hormone, tardive dyskinesia, neuroleptics malignant syndrome, body temperature disregulation and seizures.
- Very rare cases of QT prolongation have been reported in postmarketing experience.

WARNINGS AND PRECAUTIONS:

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Razvan® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

- Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. **Razvan®** should be used with caution in patients with known cardiovascular disease, and the dosage should be titrated as recommended. A dose reduction should be considered if hypotension occurs.
- Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because **Razvan®** has a lower potential to induce extrapyramidal symptoms than classical neuroleptics, it should have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia develop, discontinuation of all antipsychotic drugs is recommended.
- The Neuroleptic Malignant Syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels has been reported to occur with classical neuroleptics. In this case, all antipsychotic agents including **Razvan®** should be discontinued.
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including **Razvan®**, to patients with Lewy body dementia or parkinson's disease since they may be at increased risk of Neuroleptic Malignant Syndrome or a worsening of Parkinson-like symptoms.
- For specific dosage recommendations for elderly patients and patients with renal and liver disease, refer to dosage and administration.
- In placebo-controlled trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, including cerebrovascular accidents and transient ischemic attacks, in patients treated with risperidone compared to patients receiving placebo.
- Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.
- It is advisable to avoid excessive eating in view of the possibility of weight gain.
- **Razvan®** tablets contain:
Lactose monohydrate: If the patient has been told by the doctor that he has intolerance to some sugars, he should contact his doctor before taking this medicinal product.
- **Razvan®** 2mg tablets contain:
Sunset yellow color FCF (E110): May cause allergic reactions.
- Pregnancy and Lactation: The safety of risperidone for use during human pregnancy has not been established; yet, no tetratogenic effect of risperidone effect has been noted in any study. Risperidone should only be used during pregnancy if benefits outweigh the risks.
It has been demonstrated that risperidone and its metabolite 9-hydroxyrisperidone are excreted in human breast milk; therefore women receiving risperidone should stop breast feeding.
- Effects on ability to drive and use machines: **Razvan®** may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Special Precautions (for oral solution):
- Dilute dose before taking.
- Not compatible with cola or tea.
- May cause drowsiness.
- Avoid alcoholic beverages.

DRUG INTERACTIONS:
- Risperidone should be given with caution in combination with other centrally acting drugs.
- Risperidone may antagonize the effect of levodopa and other dopamine agonists.
- Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentration of risperidone but not those of the antipsychotic fraction.
- Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.
- Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.
- Carbamazepine or other hepatic enzyme inducers has been shown to reduce the plasma levels of the active antipsychotic fraction of risperidone.
On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of **Razvan®** should be re-evaluated and –if necessary– decreased.
- Fluoxetine and paroxetine, CYP 2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant Fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of **Razvan®**.
- Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.
- The cholinesterase inhibitors, glutamine and donepzil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.
- When risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, or digoxin.
- Food does not affect the absorption of risperidone.

DOSAGE AND ADMINISTRATION:
Schizophrenia
- Switching from other antipsychotics: when medically appropriate, gradual discontinuation of the previous treatment while initiation with **Razvan®** therapy is recommended.
Also when switching patients from depot antipsychotics, initiate **Razvan®** therapy in place of the next scheduled injection. The need for continuing existing anti-parkinson medications should be re-evaluated periodically.
- Adults: **Razvan®** can be given once or twice daily.
Patients should start with 2 mg/day. The dosage may be increased to 4 mg on the second day. From then on the dosage can be maintained unchanged, or further individualized, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.
Doses above 10 mg/day have not shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms.
The safety of doses above 16 mg/day has not been evaluated; doses above this level should be avoided. A benzodiazepine may be added to **Razvan®** when additional sedation is required.
- Elderly: **Razvan®** is well-tolerated by the elderly.
A starting dose of 0.5 mg b.i.d is recommended. This dosage can be individually adjusted with 0.5 mg b.i.d increments to 1 to 2 mg b.i.d.
- Children: Experience in schizophrenia is lacking in children aged less than 15 years.
- Renal and liver disease: A starting dose of 0.5mg b.i.d. is recommended. This dosage can be individually adjusted with 0.5 mg b.i.d. increments to 1 to 2 mg b.i.d. **Razvan®** should be used with caution in this group of patients until further experience is obtained.

Conduct and Other Disruptive Behavior Disorders
- Subjects ≥ 50 Kg: A starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg once daily while others may require 1.5 mg once daily.
- Subjects < 50 Kg: A starting dose of 0.25 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily while others may require 0.75 mg once daily.

As with all symptomatic treatments, the continued use of **Razvan®** must be evaluated and justified on an ongoing basis.
Experience is not available in children aged less than 5 years.
Instructions for use/handling:
Directions for opening the bottle and using the pipette
1. Push the plastic screw cap down while turning it counter clockwise. Remove the unscrewed cap.
2. Insert the pipette into the bottle. While holding the bottom ring, pull the top ring up to mark corresponding to the number of millilitres or milligrams you need to give
3. Holding the bottom ring, remove the entire pipette from the bottle.
Empty the pipette into any non–alcoholic drink, except for tea, by sliding the upper ring down.
Close the bottle.
Rinse the pipette with some water.

OVERDOSAGE:
- In general, symptoms associated with risperidone overdosage include: sedation, drowsiness, tachycardia, hypotension and extrapyramidal symptoms.
- Rare cases of QT-prolongation.
- Treatment: maintain clear airway, ensure adequate oxygenation and ventilation.
Gastric lavage (if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered.
Cardiovascular monitoring including electro-cardiographic monitoring to detect possible arrhythmias must be taken into account. There is no specific antidote to risperidone, so the treatment will be supportive. Hypotension and circulatory collapse should be treated with appropriate supportive measures like intravenous fluids and or sympathomimetic agents.
In case of severe extrapyramidal symptoms, anticholinergic medication should be given.
Close medical supervision should be continued until patient is recovered.

PRESENTATIONS:
Razvan® 1: Packs of 20 film coated tablets. Each tablet contains 1 mg Risperidone.
Razvan® 2: Packs of 20 film coated tablets. Each tablet contains 2 mg Risperidone.
Razvan® 3: Packs of 20 film coated tablets. Each tablet contains 3 mg Risperidone.
Razvan® 4: Packs of 20 film coated tablets. Each tablet contains 4 mg Risperidone.
Razvan® Solution: Bottles of 100 ml. Each 1 ml contains 1 mg Risperidone.

STORAGE CONDITIONS:
Store below 30°C.

This is a medicament.
- *Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.*
- *Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold you the medicament.*
- *The doctor and the pharmacist are experts in medicine, its benefits and its risks.*
- *Do not, by yourself, interrupt the period of treatment prescribed.*
- *Do not repeat the same prescription without consulting your doctor.*

Keep medicament out of reach of children

Manufactured by Dar Al Dawa, Na'ur - Jordan
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